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Is the partial pressure of carbon dioxide in the blood related to the development of retinopathy of prematurity?

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Abstract

Aims—To determine the role of carbon dioxide in the development of retinopathy of prematurity (ROP).

Methods—This was a retrospective cohort study of 25 consecutive infants admitted to the neonatal unit with continuously recorded physiological data. The daily mean and standard deviation (SD) of transcutaneous carbon dioxide partial pressure (tcPCo₂) was compared between infants who had stage 1 or 2 ROP and stage 3 ROP. The time spent hypocarbic (<3 kPa) and/or hypercarbic (>10 kPa and >12 kPa) was also compared between these groups. Intermittent arterial carbon dioxide tension was also measured and compared with the simultaneous tcPCo₂ data.

Results—There were no significant differences in carbon dioxide variability or time spent hypocarbic and/or hypercarbic between the ROP groups on any day. 86% of transcutaneous values were within 1.5 kPa of the simultaneous arterial value.

Conclusion—TcPCo₂ measurement can be a very useful management technique. However, in this cohort neither variable blood carbon dioxide tension nor duration of hypercarbia or hypocarbia in the first 2 weeks of life was associated with the development or severity of ROP.

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analysed continuous transcutaneous carbon dioxide data.

Methods

This was a retrospective cohort study of infants who were admitted to the neonatal intensive care unit, Edinburgh, between 1996 and 1998. Inclusion criteria were 14 days of continuous monitored data of transcutaneous carbon dioxide, at least stage 1 ROP, and less than 1001 g birth weight or less than 30 weeks gestation.

Infants were divided into two groups, stage 1 or 2 ROP (ROP1,2 group) and stage 3 ROP (ROP3 group). Stage 3 ROP was defined by the presence of extraretinal neovascularisation.

A computerised neonatal cot monitoring system in routine clinical use recorded physiological data including transcutaneous carbon dioxide pressure (tcPCo₂) from Hewlett Packard combined oxygen and carbon dioxide probes and 78344A neonatal monitors. The data were recorded every second and later stored as a 1 minute average of 60 one second data points. After removal of obvious artefact due to probe calibration the mean and standard deviation were calculated for each day of the first 14 days of life. For each period we also noted the number of minutes that the tcPCo₂ was under 3 kPa, was over 10 kPa, and was over 12 kPa. All values were further aggregated over a week or 2 week period to produce a single mean for each statistic for each baby. Arterial carbon dioxide (PCo₂) tension was also measured intermittently by umbilical or peripheral arterial catheter sample and compared with the simultaneous transcutaneous carbon dioxide data.

Retinopathy of prematurity was diagnosed using binocular indirect ophthalmoscopy with a speculum and scleral indentation. Careful 360° examination of the peripheral retina up to the ora serrata was performed in every instance, by one of two experienced paediatric ophthalmologists. The first examination occurred at 4-6 weeks post delivery and was repeated weekly until the retina was fully vascularised. ROP was determined using the international classification for ROP.¹³ Data from the infants who were in ROP1,2 group were compared with those who were in ROP3 group by repeated measures analysis of variance (SPSS).

For each baby on each day there was a mean value of tcPCo₂ (with artefacts excluded) and a standard deviation (SD). The SDs were then averaged as a measure of variability. The daily means and the daily standard deviations of the babies in the ROP1,2 and ROP3 groups were compared on a daily basis by *t* test and

Retinopathy of prematurity (ROP) is the most commonly acquired retinal disease in premature babies. It is multifactorial, with gestational age¹⁻³ and low birth weight¹⁻⁴ being the most powerful predictors of progression to disease. Although originally it was postulated that high arterial oxygen levels⁵⁻⁶ were causative, more recently data have shown that fluctuations in arterial blood oxygen tension⁷ are more closely related to the development and severity of the disease.

Clinical studies investigating carbon dioxide have shown both hypercarbia⁸⁻⁹ and hypocarbia¹⁰⁻¹¹ to correlate with retinopathy. Animal studies have established a link to hypercarbia,¹² but difficulty in inducing hypocarbia has made it difficult to resolve these conflicting data.

The aim of this study was to determine whether hypercarbia or hypocarbia or the variability of carbon dioxide in the first 2 weeks of life in extremely preterm infants were associated with the development of ROP. A criticism of the previous clinical studies was that they used intermittent arterial blood gas analysis to associate PCo₂ with pathology,⁸⁻¹¹ we have

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Table 1 Mean (SD) and the variability of $tcPco_2$ (in kPa) during the first 14 days of life in ROP1,2 and ROP3 group. Significance was defined as $p \leq 0.05$ however there were no significant differences between the groups on any day

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
ROP 1,2 $tcPco_2$ mean	5.3 (1.0)	5.9 (0.7)	6.1 (0.8)	6.0 (1.1)	5.9 (0.8)	6.2 (0.9)	6.6 (0.9)	6.4 (1.0)	6.1 (1.1)	6.6 (1.3)	6.8 (1.5)	6.5 (1.9)	6.8 (1.4)	7.1 (1.4)
ROP 3 $tcPco_2$ mean	5.7 (1.0)	6.1 (0.9)	6.2 (0.8)	6.4 (0.9)	6.2 (1.1)	6.2 (1.3)	6.7 (1.4)	6.8 (1.1)	6.8 (1.1)	6.9 (1.2)	7.1 (1.4)	6.7 (1.4)	6.6 (1.6)	7.1 (1.6)
ROP 1,2 $tcPco_2$ variability	1.0 (0.3)	1.0 (0.3)	0.9 (0.4)	1.0 (0.2)	1.0 (0.4)	0.9 (0.2)	1.0 (0.3)	1.0 (0.4)	1.0 (0.2)	1.0 (0.3)	0.9 (0.4)	0.8 (0.1)	0.9 (0.2)	1.0 (0.5)
ROP 3 $tcPco_2$ variability	1.3 (0.5)	1.2 (0.5)	0.9 (0.3)	0.9 (0.3)	0.8 (0.2)	0.9 (0.2)	1.0 (0.5)	1.0 (0.4)	0.9 (0.3)	1.0 (0.3)	1.0 (0.5)	0.9 (0.4)	1.0 (0.2)	0.9 (0.4)

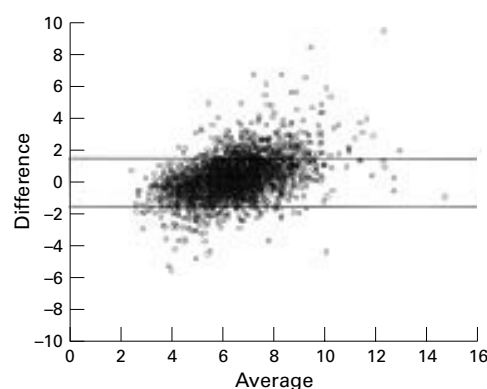


Figure 1 The comparison of transcutaneous and simultaneous arterial Pco_2 . These data are displayed as a Bland-Altman plot; 85.8% of transcutaneous values being within 1.5 kPa of the simultaneous arterial value (1.5 kPa or less difference between $tcPco_2$ and Pco_2 was accepted in this study as a satisfactory agreement.) Difference = difference between Pco_2 and $tcPco_2$ (kPa) at time of each arterial blood gas measurement. Average = mean of Pco_2 and $tcPco_2$ (kPa) at time of each arterial blood gas measurement.

throughout the study using a repeated measures ANOVA (analysis of variance). A Bonferroni correction (with significance defined as $p \leq 0.05$) was used because there were a large number of comparisons for the t test.

The time in minutes that the $tcPco_2$ was <3 kPa, >10 kPa, and >12 kPa was calculated for each infant during week 1 and again during week 2. The values in ROP1,2 group were compared with ROP3 group using a Student's t test.

Results

Over the 2 year period 50 infants were diagnosed with any stage of ROP and 25 of these babies met the inclusion criteria, the others failing mainly because of a lack of the 2 weeks of continuous monitoring data. Infants enrolled in the study had a mean birth weight of 691 g (530–1245 g) and gestational age 25.2 weeks (range 24–29). Ten were in ROP1,2 group and 15 were in ROP3 group.

There was no statistical difference between mean $tcPco_2$ values or in the variability of $tcPco_2$ during the first 14 days of life between the two groups (Table 1). The length of time that the $tcPco_2$ was under 3 kPa, was over 10 kPa, or was over 12 kPa was also not significantly different between ROP1,2 and ROP3 group in either the first or the second week of life.

Figure 1 is a Bland-Altman plot of the intermittently measured $Paco_2$ versus the simultaneous $tcPco_2$ data and the differences were not significant; 85.8% of transcutaneous values were within 1.5 kPa of the simultaneous arterial value, and a difference of ≤ 1.5 kPa between $tcPco_2$ and $Paco_2$ was accepted in this study as a satisfactory agreement.

Discussion

The present study does not support the view that either increased variability of blood carbon dioxide or a particular duration of hypercarbia or hypocarbia in the first 2 weeks of life is related to the development or severity of ROP.

In this study blood carbon dioxide levels were measured by a continuous transcutaneous monitoring system for 14 days which is in contrast with other studies that have used intermittent blood gas analysis. To ensure that the transcutaneous measurements were accurate they were compared with the simultaneous but intermittently measured arterial carbon dioxide tension. We found that agreement between the methods was usually excellent and the comparison was clinically highly satisfactory.

The transcutaneous measurements resulted in nearly 20 000 data points per baby—each of which in itself was a 1 minute average of 60 one second points. This allowed an objective analysis of the variability of blood carbon dioxide.

The number of infants enrolled in the study was small but the confidence intervals of the results suggest that the lack of difference between groups is unlikely to be related to small numbers creating a type II error. It would certainly be preferable to involve more babies, but during the 2 year period of investigation only 25 infants met the requirements of the inclusion criteria.

The known effects of carbon dioxide tension on small vessel calibre make it inappropriate to discard carbon dioxide as an important factor based on this study alone. Our group has developed an animal model of ROP based on clinically relevant fluctuations in oxygen^{14 15} and we plan to use this to investigate the combination of oxygen variability and hypercarbia on the development and severity of ROP.

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